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The Association Of Adiponectin, Homocysteine, B 12 And Folic Acid In Iraqi Women With Preeclampsia And Its Severity

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Abstract

Background: preeclampsia is a common obstetric disorder that remains a leading cause of maternal and perinatal mortality and morbidity. Maternal serum concentrations of adiponectin, folate, homocysteine, and vitamin B12 have been found to be associated with pre-eclampsia. Nevertheless, reported studies involved still not clear with variable reliably. The aim of the present study is to examine the relationship between these biomarkers and pre-eclampsia and its severity in Iraqi population. **Aims:** The study aims to evaluate the association between maternal serum adiponectin, homocysteine, B12 and Folic acid and preeclampsia and its severity.

Study design and setting. A case control study carried out in Al-Zahraa Maternity and Pediatric Teaching Hospital in Najaf city/ Iraq from the 1st of December 2019 to the 1st of December 2020. **Patient and Methods:** The study included 50 pregnant women with preeclampsia and a comparative control group of 50 normotensive pregnant women. Preeclamptic women were further subdivided into 14 women with severe preeclampsia and 36 women with mild preeclampsia. Serum Adiponectin, Homocysteine, B 12, and Folic acid were measured by using special ELIZA (Enzyme linked immunosorbent assay) technique. **Results:** There was a significant increment in the level of Adiponectin and Homocysteine while vitamin B12 and Folic acid were significantly decreased in preeclamptic pregnant women in comparison to the control group. On the other hand, there was no significant relation between the severity of preeclampsia and the level of Adiponectin, Homocysteine, Vitamin B 12, and Folic acid.

Conclusion: Women with preeclampsia had significantly lower vitamin B12 and folic acid and significantly higher concentrations of adiponectin and homocysteine than normotensive pregnant women, but no relation with its severity.

Keywords: preeclampsia, Adiponectin, Homocysteine, Vitamin B 12, and Folic acid

INTRODUCTION

Preeclampsia (PE) is a common obstetric problem of about 3–10% of all pregnancies being diagnosed as having hypertension and proteinuria after the 20th week of pregnancy. PE is primarily managed by early screening and prevention[1] as it remains a leading cause of maternal and perinatal mortality and morbidity secondary to its complications such as; eclampsia, abruptio placentae, premature birth and fetal growth retardation and are associated with significant long-term detrimental effects on both maternal and offspring cardiovascular health [2,3].

The exact mechanism underlying etiology remains unknown. There are many theories about the etiology of PE including endothelial dysfunction, inflammation and angiogenesis[4,5]. Adiponectin, a specific adipocyte derived hormone, has been considered to improve insulin sensitivity, inhibits vascular inflammation and atherosclerosis. Thus, it has been hypothesized that adiponectin may be involved in the pathophysiology of PE[6] because of its regulatory roles in trophoblast proliferation, trophoblast differentiation, trophoblast invasion of the decidua, and decidual angiogenesis[6].

An increased concentration of total circulating homocysteine in serum is recognized as an independent risk factor for cardiovascular diseases (CVD) which might be the mechanism of endothelial injury and hence vasospasm [7]. Moreover, determinants of hyperhomocysteinemia, such as low concentrations of folic acid and vitamin B_{12} involved in homocysteine metabolism are also associated with increased risk of vascular damage[8–9]. Elevated plasma homocysteine, low concentrations of vitamin B_{12} and folic acid are atherogenic factors that trigger vascular changes compatible with atherosis and endothelial dysfunction similar to the vascular changes of the placenta in PE (10,11).

Despite extensive research, conclusive evidence on the cause and consequences of PE remains to be discovered and further studies are needed. The present study aimed to determine the levels of serum Adiponectin, Homocysteine, Folic acid and vitamin B_{12} and their correlationship in Iraqi women with PE.

Materials and Methods

Study designs and setting

This prospective case control study was performed in Al-Zahraa Maternity and Pediatrics Teaching Hospital from the 1st of December 2019 to the 1st of December 2020.

Study participants and sampling: a study group of 50 women having PE with comparative control group of 50 women who have an apparently well-run, non-preeclamptic pregnant women, have been included in the present study.

Data collection: For all cases, the following data and investigations were made: maternal age, parity, gestational age, blood pressure, BMI, urinary protein, complete blood count, renal function test , liver function test , serum albumin , weight of newborn and Apgar score.

PE is diagnosed when hypertension, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, and proteinuria (2-4 +) on dipstick test appeared after 24 weeks of gestations on two occasions in previously normotensive non proteinuria women.

Then, the women with PE were classified into mild, including 36 women, and severe, including 14 women, PE according to the following criteria:

Mild PE is defined as blood pressure equals to or more than 140/90 mmHg on two occasions at least 6 hours apart and proteinuria equals to or more than 300 mg/24 hour but less than 5 g /24 hour [12]

Severe PE is diagnosed when blood pressure equals to or more than 160 systolic or equals to or more than 110 diastolic with proteinuria +3

or more in 2 random urine samples collected 4 hours apart[12].

Furthermore, severe PE is associated with: headache, visual disturbances, oliguria (less than 500 ml/24 hr), convulsions, upper abdominal pain, pulmonary oedema, elevated serum creatinine ,uric acid ,liver enzymes and thrombocytopenia[12].

Inclusion criteria

Pregnant women diagnosed as PE who have a gestational age between 20- 40 weeks of pregnancy were to be included in PE group and women who are apparently well-run uneventful pregnancy were to be included in the control group.

Exclusion criteria

Patients with chronic renal disease and auto-immune disease, patients who had meals rich in protein, patients who had essential hypertension, obesity, polycystic ovarian syndrome, insulin resistance or diabetes mellitus were all excluded.

Biochemical analysis

For measuring a complete blood count, renal function test, liver function test, serum albumin, and urinary protein, a total of 5 ml peripheral venous blood from the ante cubital vein or from the dorsum of the hand is drawn from each woman in the study by using a standard venipuncture technique. Adiponectin, Homocysteine, Vitamin B12 and Folic acid levels were estimated from the sera of patients using ELISA (Enzyme linked immunosorbent assay).

Ethical consideration: An approval for the study was obtained from the Scientific Committee in the Department of Gynecology and Obstetrics, and from the Scientific and Ethic Committee in the Faculty of Medicine / University of Kufa. The procedures included in the study were clarified to all the women and take their agreement as a verbal consent for participation in the study, including taking information, investigation, and subsequent blood aspiration.

Statistical analysis

A statistical analysis was done by using SPSS (statistical package for social sciences) version 20 in which we use ANOVA test (analysis of variance) with LSD for comparison between groups. We set p value ≤ 0.05 as significant.

The Results

The case control study including 50 pregnant patients having PE :36 with mild PE and 14 women with severe PE, with comparative control group including 50 normotensive patients. The demographic and blood pressure with proteinuria are plotted in Table (1) below. Hematological, renal, and liver enzymes, and the outcome of pregnancy like the weight of the newborn, Apgar score in 1 minute and 5 minute in the groups of the study were all compared, as in Table (1).

Table (1) A Comparison of Different Parameters between the Groups

Parameter	Controls (n=50) (A)	Mild PE (n=36) (B)	Sever PE (n=14) (C)	P value		
	Mean±SD	Mean±SD	Mean±SD	A vs. B	A vs.C	B vs. C
Age/years	26.04±5.484	26.83±7.88	32.35± 10.27	0.615	0.005	0.017
GA/weeks	38.125±1.1036	37.00±1.603	36.07±1.141	<0.001	<0.001	0.027
Systolic BP	122±6.38	142.08±7.59	185±21.75	<0.001	<0.001	<0.001
Diastolic BP	78.4±4.67	99.16±8.98	111±7.11	<0.001	<0.001	<0.001
Proteinurea	0	1	2	<0.001	<0.001	<0.001
Platelet	193.52±42.254	192.75±50.10	159.07±45.56	0.939	0.014	0.021
WBC	10.50±2.836	12.56±3.52	16.56±3.54	0.004	<0.001	<0.001
Hb g/dl	11.88±1.623	11.91±1.158	12.73±0.519	0.922	0.042	0.059
RBC	4.643±1.07	3.98±0.469	4.41±0.183	0.001	0.364	0.118
RBS mg/dl	93.62±21.979	91.74±10.8	88.98±11.75			
SGOT U/L	11.77±4.546	8.48±1.423	15.09±7.067	0.001	0.011	<0.001
SGPT U/L	8.73±3.735	8.41±3.224	8.90±7.289	0.731	0.898	0.718
Cholesterol	225.25±10.88	187.33±23.64	196.00±35.60	0.003	0.041	0.514
S.Albumin	3.391±1.105	3.11±0.389	2.93±0.213	0.168	0.169	0.609
Urea mg/dl	19.168±4.413	24.00±6.65	20.42±3.43	<0.001	0.428	0.033
Creatinine mg/dl	0.825±0.198	0.87±0.166	0.73±0.108	0.203	0.1	0.014
BMI Kg/m^2	31.31±3.559	32.25±3.21	30.21±2.66	0.199	0.279	0.055
Newborn weight	3.344±0.373	2.82±0.725	2.69±0.449	<0.001	<0.001	0.428
Apgar score1	6.32±0.843	5.33±1.0	6.00±0	0.002	0.530	0.246
Apgarscore 5	8.24±0.656	7.91±0.87	7.57±0.85	0.057	0.005	0.157

Table (2) A Comparison of Adiponectin, Homocystine, Folic acid, and vitamin B12 in the Groups of Study.

Parameter	Control (n=50) (A)	Mild PE (n=36) (B)	Severe PE (C) (n=14)	P value		
	Mean±SD	Mean±SD	Mean±SD	A vs. B	A vs. C	B vs.C
Adiponectin µ/ml	11.02±0.917	14.72±1.10	14.77±0.97	<0.001	<0.001	0.865
Homocystine µmol/L	7.34±0.926	14.79±1.19	14.25±1.32	<0.001	<0.001	0.121
Folic acid ng/ml	11.22±0.598	9.71±0.509	9.67±0.449	<0.001	<0.001	0.851
Vitamin B12 Pg/ml	432.66±46.92	352.34±40.94	345.35±39.46	<0.001	<0.001	0.616

Table (2) shows the Adiponectin serum levels with the higher levels in PE group whether mild or severe 14.72±1.10 and 14.77±0.97 and lower in control group 11.02±0.917(p-value **<0.001)**. It shows a significant increment in the level of homocysteine between preeclamptic patients either mild 14.72±1.10 or severe 14.25±1.32 and normotensive control group 7.34±0.926 as p value <0.001 for both in comparison with the control group. There was a significant decline in the level of Folic acid and B12 in both mild and severe PE (9.71±0.509, 9.67±0.449) (352.34±40.94, 345.35±39.46) in comparison to the controlled non preeclamptic women (11.22±0.598) and (432.66±46.92, p-value **<0.001)**.

Discussion

PE is closely linked to various metabolic changes, altered inflammatory responses, endothelial dysfunction and, recently, to an anti-angiogenic state (13,14,15).

The findings of the present study have indicated that the mean plasma adiponectin concentration is higher in patients with PE than in normal pregnant women, but there is no difference between severe and mild PE. They are in agreement with some previous reports like that of Hayashi M. where a sample of 15 PE patient against 23 normal pregnant women. The mean adiponectin levels where the PE group had higher concentrations of adiponectin(16). This was true for other researchers in different sample sizes like Ramsay JE et al , Haugen F et al, Hendler I et al, Kajantie E et al, Lu D et al and Naruse K et al(17,18,19, 20, 21,22). Another study done by Khosrowbeygi found that the serum levels of adiponectin were significantly higher in the preeclamptic group than those in the normal control group and that this elevation of adiponectin levels might be a physiological feedback response to minimize endothelial dysfunction in PE patients(23). This, however, contrasted other observations in which serum adiponectin concentration is lower in patients with PE than in normal pregnant women (Cortelazzi D. et.al, when he compared serum adiponectin in 5 PE with 37 healthy pregnant women, D'Anna R and Suwaki N et al) (24,25,26). Differences in the study design and sample size may contribute to the discrepancies among studies.

As the homocysteine metabolism required Folate and vitamin B12, and their deficiency can result in increased homocysteine concentration, the present study has shown a significant increase in the level of homocysteine in preeclamptic women in comparison with normotensive pregnant women and vitamin B 12 and Folic acid which were significantly decreased in PE but they does not reflect the severity of the disease. Hyperhomocysteinaemia can result from genetic or nutrient related disturbances in the transsulfuration or remethylation pathway for homocysteine metabolism. Inadequate intake of vitamin B12, B6 or folate may underlie some cases of elevated homocyst(e)ine levels. It is furthermore known that renal function plays a significant role in homocysteine catabolism and it usually affected PE. Hyperhomocysteinemia may result in vasomotor dysfunction because the amended structure and biomechanics of blood vessels and enhanced thrombosis are considered to be independent risk factors for metabolic and cardiovascular disease. The mechanism of vascular damage by homocysteine has not been fully explained, but the importance of vascular smooth muscle cell proliferation and vascular remodeling leading to thrombosis and atherosclerosis should be considered. Wang et al. [27] had shown that maternal plasma homocysteine levels are significantly higher in pregnancy with pre-eclampsia and/or umbilical placental vascular disease.

Marzena Laskowska et al [28] compare the maternal serum levels of endothelial nitric oxide synthase, asymmetric dimethylarginine (ADMA). Homocysteine in normal and preeclamptic pregnancies shows that serum concentrations of homocysteine and ADMA were increased in both early onset and late onset PE. An additional study done by Shahid A. et al [29] also shows that there was significant hyperhomocysteinemia in patients with PE.

Another study done by Şanlıkan F.et al[30]shows that mean serum Homocysteine level was significantly higher in the preeclamptic group as compared to controls but there were no statistically significant differences in Homocysteine levels between mild and severe PE groups. In addition, Atis et al[31] also measured serum Homocysteine in women with mild and severe preeclamptic pregnant women and found that Homocysteine increases in PE, but the severity of PE is not correlated with homocysteine levels while a study done by Ingec et al[32] shows that plasma homocysteine significantly elevated in severe PE not in mild ones.

Stoĭkova et al[33] study finds a link between the serum homocysteine as an endothelial dysfunction marker and the development of PE and a relation between the severity of PE and the degree of the elevation of the serum homocysteine levels. Kharb study folate, vitamin B12 and homocysteine levels in cord blood and maternal blood in PE found elevated homocysteine and folate and vitamin B12 deficiency during pregnancy may be a risk factor for PE and future cardiovascular risk[34]. On the other hand, Nahid Shahbazian, Women with PE displayed higher maternal serum homocysteine and lower serum folate and vitamin B12 levels(35) while Acilmis YG et al concluded that maternal and fetal serum homocysteine levels were found to be significantly higher in severe pre-eclampsia group compared to mild pre-eclampsia and control groups suggesting that elevated serum levels of homocysteine might be associated with severity of pre-eclampsia but the elevated serum homocysteine levels were not associated with deficiency of folic acid and vitamin B12(36) and Makedos G[37] et al concluded that homocysteine levels are significantly elevated in patients with PE compared with control group, while no vitamin deficiencies were observed. Malahayati et al[38] found that

Low folic acid levels tend to increase homocysteine levels in severe PE, whereas high folic acid levels tend to lower homocysteine levels in normal pregnancy.

Conclusions

Serum Adiponectin and Homocysteine were significantly increased, and Vitamin B 12 and Folic acid were significantly decreased in PE but they do not reflect the severity of the disease.

Recommendations

1- Further studies are needed to confirm if the prescription of folic acid and vitamin B12 in women deficient in these vitamins could decrease the level of serum homocysteine, thereby reducing the risk of PE or (if it occurs) its severity.

2- Further studies should help define the role of genetic polymorphism in enzymes of homocysteine, folic acid, vitamin B_{12} metabolism and their role in PE.

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Competing interests

The authors declare that there is no conflict of interest.

Author Contributions

The authors wrote, read and approved the final manuscript.

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